REMARKS

I. Status of the Claims

Claims 1-25 were originally filed. As the result of a restriction requirement, claims 13-25 have been withdrawn and later canceled. Claim 6 was subsequently canceled. Upon entry of the present amendment, claims 2-4 are further canceled. Claim 1 is amended to recite the limitation from claim 4, "wherein said plurality of heterologous antibodies comprises ten said heterologous antibodies."

This amendment was not filed earlier because Applicants in good faith believed that this particular amendment was not necessary to overcome the claim rejections raised in the previous Office Action. Since this amendment introduces no new matter and requires no new search, the entry of this amendment is respectfully requested.

II. Claim Rejections

A. 35 U.S.C. §102

Luka et al.

Claims 1-3 and 8 were rejected under 35 U.S.C. §102(b) for alleged anticipation by Luka *et al.* Applicants respectfully traverse the rejection, particularly in light of the present amendment.

As amended, claim 1 recites all limitations of claim 4, which is now canceled. Because claim 4 was not rejected for alleged anticipation by Luka *et al.*, Applicants submit that the anticipation rejection of claim 1 (and its dependent claim 8) is overcome.

Wong et al.

Claims 1, 4, and 5 were rejected under 35 U.S.C. §102(b) for alleged anticipation by Wong *et al.* Applicants respectfully traverse the rejection, particularly in light of the present amendment and the Rule 132 declaration by Dr. Peilin Chen.

1. The Wong Reference Does not Anticipate the Pending Claims

To anticipate a pending claim, a prior art reference must provide, either expressly or inherently, each and every limitation of the pending claim. MPEP §2131. As amended, claim 1 now recites an additional limitation: the claimed composition should comprises at least ten heterologous antibodies.

The Examiner cited the Wong reference as the basis to support the anticipation rejection. It was not pointed out, however, where in the Wong reference can one find the limitation of having ten or more different antibodies in a composition. Instead, the Examiner merely stated that "one would expect that Wong's multiple antibody calibrator composition would contain numerous antibodies to different pathogens since Wong discloses that a plurality of antibodies can be used in one assay." See page 4, lines 1-3, of the Final Office Action mailed July 26, 2005.

Applicants do not believe that the alleged anticipation by the Wong reference has been properly established. First, the Wong reference fails to expressly provide the limitation of ten or more antibodies present in a composition. Secondly, the reference also fails to inherently disclose this limitation. As set forth by the Board, "in relying upon the theory of inherency, the Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Int. 1990). In the present case, no such basis has been provided. Quite to the contrary, the Wong reference merely describes a calibrator containing antibodies that can recognize more than one organism. This description simply does not inherently, or necessarily, discloses ten or more different antibodies in the same composition.

2. The Wong Reference Does Not Render the Pending Claims Obvious

Furthermore, Applicants contend that a calibrator of the present invention that contains ten or more different antibodies is not obvious over a calibrator containing a fewer number (*e.g.*, four or five) of different antibodies. To this end, a declaration under 37 C.F.R.

§1.132 by Dr. Peilin Chen, a named inventor on this application, has been provided to establish non-obviousness.

In his declaration, Dr. Chen states that, while it is relatively easy to construct a calibrator that is designed for individual immunological assays and contains antibodies for up to four or five distinct antigen specificities, it is increasingly difficult to include additional antibodies of different antigen specificities in the calibrator for a multiplexing immunoassay, due to the instability of an antibody solution at a high total antibody concentration, as well as the dilution effect caused by mixing multiple sera containing antibodies of desired specificities. When one combines ten or more different antibodies, there is no reasonable expectation of success that a functional calibrator will be produced (paragraph 5 of the declaration).

Dr. Chen explains that the difficulties in making multi-specificity calibrators directly relate to the properties of antibodies. Antibodies are relatively large glycoproteins that consist of two light chains and two heavy chains. The average molecular weight of a monomer human IgG antibody is about 150 kDa, whereas a pentamer human IgM is about 950 kDa. Synthetic antibodies, such as those used in the calibrator of the Wong reference, have an average molecular weight of over 1,000 kDa. Through the variable regions located near the N-terminus of the light and heavy chains, antibodies bind with specificity to their respective antigens. Through the constant regions near the C-terminus of the heavy chains, antibodies bind with other proteins such as Fc receptors and components of the complement pathway. Because of their high molecular weight and their propensity to bind to various other molecules, antibodies are more likely to form aggregates and/or precipitate from a solution when their combined concentration reaches a certain level (paragraph 6 of the declaration).

When one starts with a calibrator containing four or five different antibodies, each present at a level that is sufficient to allow detection through its complex with its corresponding antigen, to include additional antibodies into the calibrator, it becomes more and more difficult as the number of the antibodies increases. As these additional antibodies are introduced into the serum, each of such additional antibodies must also reach a level that is sufficient for detection

through antigen-antibody complexing. To ensure that the antibodies remain dissolved in the serum, these antibodies combinedly must also remain below the concentration where antibody aggregates form or antibodies precipitate from the solution and the resulting composition becomes non-functional as a calibrator (paragraph 7 of the declaration).

According to Dr. Chen, a further difficulty associated with the construction of a multi-antibody calibrator relates to the dilution effect caused by mixing multiple sera containing antibodies of desired specificities. When antibodies present in multiple sources (*e.g.*, multiple sera) are simply mixed, especially when the number of antibodies is large (*e.g.*, ten or more), each of the antibodies will inevitably become overly diluted and fall below the necessary concentration for detection. Thus, there is no reasonable expectation to successfully construct a functional calibrator containing ten or more different antibodies (paragraph 8 of the declaration).

In contrast to the difficulties in constructing a calibrator containing antibodies that have ten or more different antigen specificities and remain dissolved in a serum, Dr. Chen attests that the present inventors have in fact successfully assembled several IgG and IgM calibrators, each of which containing antibodies with specificities against more than ten different antigens derived from microorganisms including *Toxoplasma gondii*, Rubella virus, Cytomegalovirus (CMV), Herpes Simplex Virus type-1 (HSV-1), Herpes Simplex Virus type-2 (HSV-2), Mumps Virus, Measles Virus, Epstein-Barr Virus (EBV), Varicella Zoster Virus, *Borrelia burgdorferi*, *Treponema pallidum*, *Helicobacter pylori*, and *Mycoplasma pneumoniae*. These calibrators have been shown in actual testing to be fully functional as calibrators or positive controls for multi-analyte immunological assays. This is the first time that anyone has successfully produced a useable calibrator containing antibodies with more than ten antigen specificities (paragraph 9 of the declaration).

The Rule 132 declaration by Dr. Chen thus establishes that the multi-antibody composition of the present invention is not obvious in view of the Wong reference, due to the difficulties associated with constructing a functional multi-specificity calibrator and therefore the

lack of any reasonable expectation that a functional multi-specificity calibrator can be readily made.

In summary, the Wong *et al.* reference neither anticipates the pending claims nor renders the claims obvious. The withdrawal of the rejection under 35 U.S.C. §102(b) is respectfully requested.

B. 35 U.S.C. §103

In the Final Office Action mailed July 26, 2005, the Examiner sustained the following rejections: claim 10 was rejected under 35 U.S.C. §103(a) for alleged obviousness over Wong *et al.* in view of Desmonts *et al.*; claims 9 and 11 were rejected under 35 U.S.C. §103(a) for alleged obviousness over Wong *et al.* in view of Desmonts *et al.* and further in view of Gans *et al.*, Yi *et al.*, Krell *et al.*, and Luka *et al*; and claim 12 was rejected under 35 U.S.C. §103(a) for alleged obviousness over Wong *et al.* in view of Desmonts *et al.*, Gans *et al.*, Yi *et al.*, Krell *et al.*, Luka *et al.*, and Lo *et al.* Applicants respectfully traverse these rejections.

As discussed above, the primary reference by Wong *et al.* fails to provide, either expressly or inherently, all limitations of claim 1 in its current, amended version. Furthermore, Dr. Chen's declaration establishes that, when one adds ten or more antibodies into one serum, there is no reasonable expectation of success that a functional calibrator can be readily produced. Thus, the Wong *et al.* reference neither anticipates claim 1 nor renders it obvious. Because the secondary references (Desmonts *et al.*, Gans *et al.*, Yi *et al.*, Krell *et al.*, Luka *et al.*, and Lo *et al.*) merely supply additional limitations recited in the dependent claims and are not directly relevant to claim 1, the primary and second references, when viewed together, cannot render dependent claims 9-12 obvious.

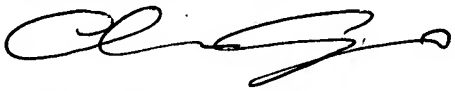
It is respectfully requested that the Examiner reconsider and withdraw the obviousness rejection under 35 U.S.C. §103.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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